antibodies in SCLC patients without LES has to be further investigated in a larger population to better define their possible pathogenetic role. None of the myasthenic patients tested had anti-VOCC antibodies, whereas 1 LES patient had also antinicotinic receptor antibodies, which suggests the possibility of a combined myasthenic syndrome,[1] at least at the immunochemical level. Use of this new immunoassay to screen a larger number of myasthenia gravis patients will allow the detection of cases in which LES occurs together with myasthenia gravis.

Antigenic modulation is a common mechanism by which anti-receptor antibodies down-regulate the number of receptors expressed at the cell surface, and this effect is important for explaining the biological and clinical activity of the autoantibodies.[30] LES antibodies clearly recognise antigenic determinants on the VOCC which are "external" to the site where ωCTx binds, since, for the purpose of the immunoassay, this site was already occupied by the toxin. Furthermore, LES autoantibodies were not able to directly inhibit ^{125}I-ωCtx binding to IMR32 membranes. However, LES antibodies were able to down-regulate the expression of VOCCs in IMR32. This effect was highly specific with respect to other membrane molecules such as the α-Bgtx receptor. However, we cannot exclude the possibility that different patients synthesise different antibodies with different specificities and mechanisms of action, as in the case of antibodies against nicotinic receptors in myasthenia gravis.

We thank Dr V. A. Lennon for allowing us to perform the blind experiment, for the permission to use these results, and for help with the manuscript; Dr L. Rosenthal for helping to improve the paper; Prof G. Fumagalli for his critical suggestions; Dr F. Baggi for help with antinicotinic receptor antibody assays; and Mr P. Tinelli for technical collaboration.

This work was partly funded by the CNR Special Project "Neurobiology".

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SMOKING AS A RISK FACTOR FOR CEREBRAL ISCHAEMIA

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Summary To assess whether a rigorous clinical classification, based on computerised tomography, of patients with cerebral ischaemia would identify subgroups at higher or lower risk with respect to cigarette smoking habits, a case-control study was carried out on 422 cases of first-episode cerebral ischaemia matched for age and sex with 422 community-based neighbourhood controls. Patients with ischaemic stroke due to extracranial or intracranial vascular disease were at higher risk from smoking than has previously been reported for stroke (relative risk 5·7, 95% confidence interval 2·8, 12·0) whereas those with stroke due to cardiac emboli had no excess risk associated with smoking (relative risk 0·4 [0·1, 1·8]). After cessation of smoking, the relative risk declined gradually over 10 years, at the end of which time a significant risk was still evident. This finding may imply that the risk incurred by smoking is due mainly to atheroma formation, rather than transient haematological effects. Exposure to smoking by a spouse was an independent risk factor for the whole group of cerebral ischaemia patients (relative risk 1·7 [1·1, 2·6]), but this was not so for smoking by either parent (relative

E. SHER AND OTHERS: REFERENCES—*continued*

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risk 1·2 [0·8, 1·8]). These findings suggest that smoking is a more potent risk factor for the most common form of ischaemic stroke than has previously been appreciated. The persistent nature of the risk even after cessation of smoking and the possible risk associated with passive exposure strengthens public health arguments against smoking.

Introduction

THE clinical picture of stroke can be produced by several pathophysiological mechanisms, the most important of which are atherothrombotic brain infarction, intracerebral haemorrhage, and subarachnoid haemorrhage. Before the development of computerised tomography (CT), the diagnosis of undifferentiated "stroke" was often contaminated by other causes of acute, focal neurological deficits, such as cerebral neoplasm, subdural haematoma, and cerebral abscess. Furthermore, the discrimination between pathophysiological subtypes was difficult. CT scanning, now established as a routine diagnostic procedure in most developed countries, provides an accurate and non-invasive means of subgrouping stroke types.

Risk factors for stroke have been identified in various epidemiological studies. Most were carried out before CT became available and attributed hypertension and ageing as the primary antecedents.[1,2] Cigarette smoking, which is associated with atheroma generation elsewhere in the body, has been less consistently implicated as a major risk factor for stroke, although the latest studies have shown a more convincing association.[3-7]

Our aim was to examine the risk relation between cigarette smoking and subtypes of cerebral ischaemia whose pathogenesis is related to atherosclerotic change in major cranial and extracranial blood vessels. The hypothesis examined was that, without the possible diluting effect of cerebral haemorrhage and other non-thromboembolic causes of stroke, the stroke risk associated with cigarette smoking would be greater than that reported previously and that there may be subgroups with very high risk. We also took the opportunity to examine the effects of stopping smoking on any observed risk for cerebral ischaemia, together with any independent risk which may be attributable to smoking among other family members.

Patients and Methods

Nurse-interviews identified cases of acute cerebral ischaemia in four major hospitals serving the north-eastern region of Melbourne between 1985 and 1988. These hospitals manage most such cases in this area, the exception being the very old, who may be managed at home, in smaller private hospitals, or in nursing homes.

Patients were enrolled in the study if the clinical event was their first episode of cerebral ischaemia. Patients who died were included in the study by interview of closest relatives. The duration of cerebral ischaemia was defined to range from 24 h or less (transient ischaemic attack [TIA]) to a permanent deficit (cerebral infarction). There was no age restriction for study entry. CT scans were carried out on 98% of cases within 10 days of hospital admission. Those who did not receive CT scans were elderly, in a moribund state on admission, had cerebral ischaemia diagnosed on clinical grounds by the stuttering nature of the progressive deficit, and died shortly afterwards. Patients in whom cerebral haemorrhage was shown on CT were excluded from the study.

Patients were asked to take part in a study of previous diet and lifestyle factors. A structured questionnaire was used to record information about personal characteristics, habits such as cigarette smoking, alcohol consumption, past dietary and exercise practices, and medical history (including that of treated hypertension). A detailed list of current and past drugs was used to validate information about medical history. The section of the questionnaire about smoking sought information on current consumption, previous consumption in decades, type of cigarette, cigar, or pipe smoked, and degree of inhalation. The time since stopping smoking was recorded in periods of 2 years and then 5 years from the last cigarette to increase the reliability of recall. For the effects of passive smoking among other family members, patients were asked whether mother, father, or spouse smoked as many as 1 cigarette per day for as long as 1 year and, if so, what was the highest number smoked regularly for as long as 1 year. The latter was recorded as cigarettes per day in amounts of 10.

Controls were matched individually by age (±5 years) and sex and were identified by knocking on doors in the same street (according to a strict protocol) until a household with a matching individual free of previous cerebrovascular disease was found. When an identified control was absent from the household, the interviewer returned on at least two further occasions to attempt contact. About 10% of identified controls refused to participate or could not be contacted and in these cases the next suitable neighbourhood control was chosen.

Each case and matching control were interviewed by the same nurse-interviewer. Only 1% of cases refused interview. In approximately 20% of cases communication was restricted and the closest available relative was interviewed; the closest available relative of the matched control was interviewed to avoid information bias. Most patients were interviewed while in hospital, but about 5% were interviewed at home because of rapid discharge from hospital.

The relative risk of cerebral ischaemia was estimated for subjects in various categories of smoking history, with the group who had never smoked as the reference category. Initially, unadjusted relative risks were calculated with paired data and then potentially confounding variables were controlled for by means of a conditional logistic regression model.[8] Estimates of the relative risk associated with smoking were then made for the various categories of cerebral ischaemia with correction for hypertension and the small residual effect of age.

Definitions

Smoking categories.—We defined an ever smoker as a person who smoked at least 1 cigarette, cigar, or pipe per day for at least 3 months at some period during his or her life, a current smoker as a person smoking at least 1 cigarette, cigar, or pipe per day for the preceding 3 months, and an ex-smoker as a person who met the criteria for an ever smoker, but had not smoked for the preceding 3 months. The category never smoked included people who were not current smokers and who did not meet the criteria for ex-smoker or ever smoker.

Cerebral ischaemia was defined as acute onset of a focal neurological deficit in which CT scan excluded causes other than cerebral ischaemia; the duration of ischaemia could be 24 h or less (TIA), or longer than 24 h (cerebral infarction).

Lacunar syndrome was acute onset of one of the five recognised lacunar syndromes[9] (pure motor hemiplegia, ataxic hemiparesis, dysarthria clumsy hand syndrome, sensorimotor stroke, and pure sensory stroke) in which CT had excluded underlying cerebral haemorrhage. In many cases the site of infarction was identified on CT scan, but this was not an absolute requirement for classification as a lacunar syndrome.

Thromboembolic infarction was defined as acute onset of focal neurological deficit with documentation of the site of infarction on CT scan in either cerebral hemispheres or hind brain, in which the mechanism of infarction was attributed to large vessel extracranial or intracranial vascular disease.

Cardiac embolic cerebral infarction was the acute onset of a focal neurological deficit in which the site of infarction had been documented on CT scan in the presence of atrial fibrillation, myocardial infarction within the preceding 3 weeks, or cardiomyopathy. In some cases cerebral angiography or non-invasive studies of the extracranial circulation were done to help exclude carotid occlusive disease as a causal mechanism, but this was not an absolute requirement.

TABLE I—AGE DISTRIBUTION OF 422 CASES AND CONTROLS

Age (yr)	Cases	Controls
< 40	16	17
40–44	11	14
45–49	15	17
50–54	22	21
55–59	35	37
60–64	70	66
65–69	75	87
70–74	98	87
75–79	61	51
≥ 80	19	25

Cerebral infarct site or mechanism uncertain.—This group had acute onset of a focal neurological deficit in which the site of infarction or the mechanism of its genesis was unclear but causes other than vascular causes were excluded by CT scan.

Hypertension was defined as a history of hypertension documented by a medical practitioner or current use of antihypertensive drugs recorded at interview.

High cholesterol was defined as a plasma concentration of 5·5 mmol/l or greater.

Results

The 422 consecutive patients and their matched controls were of mean age 65 years (range 25–85 in patients, 20–87 in controls; table I). There were 256 men and 166 women in each group. The relative risk (crude) of cerebral ischaemia for all factors which might have a confounding effect on smoking as a risk factor are shown in table II. These factors were controlled for by means of multiple logistic regression analysis.[8] Smoking, hypertension, and a history of myocardial infarction were significant and independent risk factors, whereas alcohol consumption seemed to have a modest but significant protective effect. Since adjustment for all risk factors made little additional difference to the overall relative risks, adjustment for hypertension and age only was made for the rest of the analysis. Hence, the relative risk of cerebral ischaemia was 3·7 (95% confidence interval [CI] 2·3, 5·9) for current smokers and 2·0 (1·3, 3·1) for ex-smokers, both compared with those who had never smoked (adjusted for age and hypertension only). Both risks were significant ($\chi^2 = 30·0$ and 11·0, respectively, each for 1 degree of freedom [df], $p < 0·001$ and $p < 0·01$). In women the risk for current compared with never smoking was 3·2 (1·6, 6·6), whereas in men the risk was slightly higher (3·8 [2·1, 7·0]); this difference was not significant ($\chi^2 = 0·1$ for 1 df, NS). Similarly, there was no difference between the sexes for ex-smoking risk (relative risk for men 1·8 [1·1, 3·1] and women 3·0 [1·3, 7·1]; $\chi^2 = 1·0$ for 1 df, NS).

The stroke risk was greatest in the group aged 55–64 years and the risk of stroke was significantly higher for current smokers under the age of 65 years than for those of 65 years or older (relative risk 6·8 [3·1, 15·0] *vs* 2·4 [1·2, 4·3]; $\chi^2 = 4·8$ for 1 df, $p < 0·05$). However, when the two groups in which smoking was not a risk factor (cardiac embolic and cerebral infarct with site or mechanism uncertain) were excluded from the analysis the difference was no longer apparent ($\chi^2 = 3·3$ for 1 df, NS). The mean ages of the cardiac embolic group (69 years) and the cerebral infarct, site or mechanism unknown group (68 years) were greater than that of the other groups (64 years).

There was a positive dose-response effect in that the risk of stroke among current smokers rose with the amount smoked. Two current smokers of the same age and hypertension status and whose daily consumption differed by one pack (20 cigarettes per day) were estimated to have a risk differing by 2·1 (1·1, 3·8; χ^2 for linear trend = 6·7 for 1 df, $p < 0·01$).

TABLE II—CRUDE AND ADJUSTED RISKS OF CEREBRAL ISCHAEMIA FOR ALL FACTORS EXAMINED BY MULTIPLE LOGISTIC REGRESSION

—	No (%)*		Estimated risk	
	Cases	Controls	Crude	Adjusted (95% CI)§
Current smoker	135 (32%)	78 (18%)	3·2	3·6 (2·2, 5·9)
Ex-smoker	145 (34%)	137 (32%)	1·9	2·0 (1·3, 3·2)
Never smoked	142 (34%)	207 (49%)	1·0	1·0
Hypertension	281 (67%)	145 (34%)	4·2	4·7 (3·2, 6·8)
High cholesterol	45 (14%)	37 (11%)	1·6	1·3 (0·7, 2·5)
Myocardial infarction	84 (20%)	50 (12%)	1·9	1·6 (1·0, 2·5)
Alcohol consumption†	252 (68%)	274 (75%)	0·6	0·6 (0·4, 1·0)
Oral contraceptives‡	31 (19%)	39 (23%)	1·0	0·9 (0·4, 2·6)

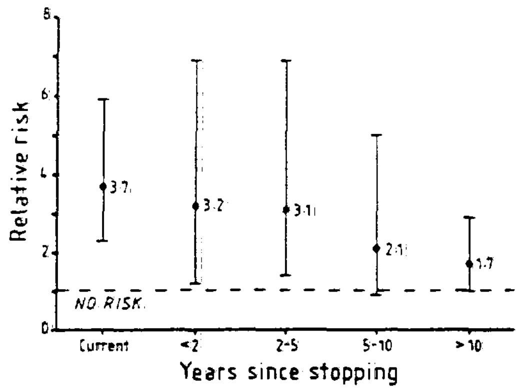
*Of subjects whose risk factor status was known.
†Yes or no.
‡Includes past as well as present use.
§Adjusted for all other risk factors.

The distribution of patients within each category of cerebral ischaemia with reference to smoking status is shown in table III. For current smokers, the greatest effect on stroke risk was for thromboembolic and lacunar stroke combined; the relative risk in this group was 5·7 (2·8, 12·0; $\chi^2 = 25·0$ for 1 df, $p < 0·001$). Patients with lacunar stroke alone had the highest relative risk associated with current smoking of all subgroups (infinite [3·0, infinity]); this risk was significantly higher than that for all other groups combined ($\chi^2 = 7·7$ for 2 df, $p < 0·05$), but only 10 matched pairs were available for analysis (the analysis method ignores pairs in which smoking status of case and control are the same) and this result should therefore be interpreted with caution. There was no risk associated with either current smoking or ex-smoking in the patients with cerebral infarction presumed to be due to cardiac emboli and patients in whom the site or mechanism of infarction was uncertain (table III). However, current smoking was a significant risk factor for TIAs (5·2 [2·1, 13·0]; $\chi^2 = 13·0$ for 1 df, $p < 0·001$).

TABLE III—NUMBERS OF PATIENTS AND MATCHED CONTROLS IN EACH CLINICAL SUBGROUP OF CEREBRAL ISCHAEMIA WITH RESPECT TO SMOKING STATUS AND RELATIVE RISKS

Subgroup	No (%)			Relative risk of cerebral ischaemia* (95% CI)
	Current smokers	Ex-smokers	Never smoked	
TIA (n = 120)				
Cases	35 (29%)	53 (44%)	32 (27%)	5·2 (2·1, 13·0)
Controls	21 (18%)	42 (35%)	57 (47%)	
Thromboembolic (n = 163)				
Cases	59 (36%)	54 (33%)	50 (31%)	5·0 (2·3, 11·0)
Controls	36 (22%)	49 (30%)	78 (48%)	
Lacunar (n = 56)				
Cases	25 (45%)	13 (23%)	18 (32%)	Inf (3·0, Inf)
Controls	7 (13%)	19 (34%)	30 (54%)	
Cardiac embolic (n = 46)				
Cases	7 (15%)	14 (30%)	25 (54%)	0·4 (0·1, 1·8)
Controls	8 (17%)	15 (33%)	23 (50%)	
Site/mechanism uncertain (n = 37)				
Cases	9 (24%)	11 (30%)	17 (46%)	0·9 (0·2, 3·5)
Controls	6 (16%)	12 (32%)	19 (51%)	
Total				
Cases	135 (32%)	145 (34%)	142 (34%)	
Controls	78 (18%)	137 (32%)	207 (49%)	

*Current *vs* never smoked.
Inf = infinity.



Effect of stopping smoking on relative risk of cerebral ischaemia.

Relative risk for each interval with 95% CI.

When the period since stopping smoking was divided into five intervals up to 10 years after stopping, a trend towards reduction in relative risk was seen (see accompanying figure). However, this trend was not significant ($\chi^2 = 0{\cdot}5$ for 1 df, NS) and an appreciable risk was still apparent after 10 years.

The effect of passive smoking as a risk factor for cerebral ischaemia was assessed for each parent and for spouse. After control for the subjects' own smoking, hypertension, and the residual effect for age, smoking by the spouse increased the risk of stroke 1·7-fold (1·2, 2·6; $\chi^2 = 7{\cdot}8$ for 1 df, $p < 0{\cdot}01$), whereas smoking by a parent increased the risk 1·2-fold (0·8, 1·8; $\chi^2 = 1{\cdot}2$ for 1 df, NS). The effect of a smoking spouse was slightly higher after exclusion of the two groups in which current smoking was not a risk factor (cardiac embolic and site or mechanism unknown). The relative risk for the remainder was 1·9 (1·2, 3·0). However, because we thought the observed effect of smoking by the spouse could be explained by current smokers with a smoking spouse tending to smoke more than those without, a further control for daily cigarette consumption of current smokers was introduced; this control did not change the estimates of relative risk for either parent or spouse. There appeared to be a positive dose-response effect in that the risk was increased by 1·3 per pack smoked by the spouse per day (χ^2 for trend = 4·8 for 1 df, $p < 0{\cdot}05$). However, for never smokers only among the cases and matched controls, the relative risk associated with a smoking spouse was slightly lower (1·6 [0·6, 3·9]; $\chi^2 = 1{\cdot}1$ for 1 df, NS), perhaps because only 88 matched pairs remained for analysis, and smoking by either parent was not a risk factor (relative risk 1·0, [0·5, 2·1]).

Discussion

The large number of cases and the high diagnostic precision by use of CT scanning in 98% of our cases has allowed us to extend the findings of previous studies in several important ways. First, in this "pure" sample of patients with cerebral ischaemia, not contaminated with other forms of "stroke", the relative risk associated with smoking was somewhat higher than that in other cohort[4-6] and case-control[3,7] studies. In four of those studies[3-6] the use of CT scan was infrequent or not stated and the possibility that non-strokes as well as cerebral haemorrhages may have contaminated the sample is therefore higher. In the only case-control study in which the clinical and CT entry criteria were similar to our own, outpatient medical clinic rather than community-based controls were used.[7] Medical outpatient control groups are likely to be contaminated with smoking-related diseases, which may partly account for the lower relative risk found in that study. Second, in the two most common forms of stroke due to extracranial or intracranial vascular disease (lacunar and thromboembolic infarction) the relative risk associated with smoking was even higher, at five to six times that of those who had never smoked, and was of the same order of magnitude as treated hypertension as a risk factor. Third, the large number of cases in our study has enabled us to examine the nature of the relation between smoking and cerebral ischaemia in more detail than has been possible previously, particularly the effects of age and stopping smoking.

There are various mechanisms by which smoking may increase the risk of cerebral ischaemia. Smoking is known to increase platelet adhesiveness[10] and fibrinogen levels and therefore blood viscosity.[11] Cerebral blood flow is reduced in chronic smokers,[12] perhaps because of the higher blood viscosity, but also vascular resistance may be greater because of the atherogenic properties of smoking.[13]

Our finding of an overall three to four times greater risk of cerebral ischaemia for smokers compared with non-smokers is similar to that reported for myocardial infarction,[14] and higher than the two to three times greater risk previously reported for "stroke".[3-7] The five to six fold increase in risk for lacunar and thromboembolic infarction is closer to that reported for peripheral vascular disease, in which one study reported an eight to nine fold increase in risk.[15] In both myocardial infarction and peripheral vascular disease, the pathogenesis relates predominantly to atheromatous changes, so the similarly sized risks with pure forms of cerebral ischaemia would be expected.

Examination of other subgroups in our study showed that smoking is also a potent risk factor for TIAs. This finding confirms the general belief that cerebral ischaemia of brief or prolonged duration has a common underlying mechanism and hence similar risk factors. The reason for the lack of risk associated with smoking in the cardiac embolic group is uncertain, but a large proportion of this group had strokes secondary to atrial fibrillation, a cardiac disorder which is not associated with smoking as a risk factor.[16] In the site and mechanism uncertain group the risk associated with smoking was also negligible. This finding emphasises the importance of a precise classification of stroke subtypes, since the group would otherwise contaminate the more clearly defined lacunar and thromboembolic groups. Although numbers were small (56 patients), the finding of a highly significant risk associated with smoking in the lacunar group compared with all other groups combined suggests that further study of the effects of smoking on small cerebral vessel disease may be useful. In the only other study to examine smoking as a risk factor for lacunar infarction,[17] the relative risk was 2·3, but that study used hospital-based controls and current smokers were not analysed separately.

Given the positive dose-response effect of smoking on risk of cerebral ischaemia and the likelihood that atherogenesis may be at least partly the reason for this, it was somewhat surprising to find that patients younger than 65 years were at greater risk than those over 65 years. However, when the two groups in whom smoking was not a risk factor (cardiac embolic and site or mechanism uncertain groups) were excluded from the analysis, this differential in risk with age was lost. This finding is most likely due to the greater age of

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patients in whom stroke was due to atrial fibrillation in our study (69 years, compared with 64 years for the remainder), and the fact that smoking is not a risk factor for this rhythm disturbance.[16] A significant risk differential with age for smoking and stroke has not been shown in previous studies, although in a meta-analysis of all known published studies on smoking and stroke, a significantly reduced risk with increasing age was shown.[18] In view of our findings, and the fact that pathophysiological subgroups of stroke were not classified in most of the published studies, this effect in the meta-analysis may well be due to the unrecognised presence of elderly patients with atrial fibrillation as a stroke mechanism. In other words, there may not be an age effect in patients with cerebral infarction due to extracranial or intracranial vascular disease.

The persistence of the risk of cerebral ischaemia for at least 10 years after stopping smoking was surprising, since in the two cohort studies that addressed this question,[5,6] the risk was found to return to that of never smokers within 2–5 years. However, in both those studies the number of patients who actually stopped smoking was much smaller and no distinction was made between cerebral haemorrhage and infarction in this part of the analysis. Since the known effects of smoking on platelet adhesiveness, fibrinogen levels, and blood viscosity are reversible within a short period, it seems likely that atherogenesis causes the persistence of risk as well as the major part of risk associated with current smoking.

The presence of a smoking spouse appeared to be an independent risk factor for cerebral ischaemia when all patients (smokers and non-smokers) were included in the analysis. A positive dose-response effect was observed for this risk with the number of cigarettes smoked by the spouse and the risk was more evident when cerebral ischaemia due only to extracranial or intracranial vascular disease was analysed. However, for non-smokers alone, there was a similar but non-significant increase in risk perhaps because of the restriction to fewer matched pairs in the analysis. Considering these two analytical methods together, it appears likely that passive smoking has a small effect. Since passive smoking is now such an important social issue, and has been shown to be a risk factor for non-smokers for other diseases[19] our preliminary findings on this subject certainly warrant further study.

This study was supported by a grant from the Tobacco Research Foundation of Australia.

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PERCUTANEOUS CORONARY EXCIMER LASER ANGIOPLASTY: INITIAL CLINICAL RESULTS

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Summary A novel 1·3 mm diameter laser catheter, consisting of 20 concentric 100 µm quartz fibres around a central lumen for a 0·35 mm flexible guide wire, was used to ablate atherosclerotic tissue in thirty patients with coronary artery disease. The laser catheter was coupled to an excimer laser delivering energy at a wavelength of 308 nm and a pulsewidth of 60 ns. The primary success rate was 90% (27 of 30 lesions). The mean (SD) percentage stenosis fell from 85 (15)% to 41 (19)% after laser ablation. In ten patients the lumen diameter after laser angioplasty was considered sufficient, but subsequent balloon angioplasty was carried out for the other twenty patients. Failure to pass the lesion was caused by vessel kinking in two patients and a total occlusion in one patient. No complications directly attributable to laser ablation, such as vessel wall perforation, occurred; one dissection occurred but had no clinical sequelae. There was one early reocclusion and death in a patient with triple vessel disease and unstable angina, probably as a result of plaque rupture after balloon angioplasty. These results are encouraging and justify further clinical investigations.

Introduction

PERCUTANEOUS transluminal coronary angioplasty has been widely accepted as treatment for coronary artery disease.[1,2] Restenosis, however, greatly limits the clinical efficacy of balloon angioplasty.[3-5] The use of laser energy transmitted through flexible fibreoptic fibres may be a possible adjunct or alternative to conventional angioplasty, because it removes atherosclerotic tissue or thrombus by vaporisation rather than by stretching and fracturing of the stenosis as in balloon angioplasty.[6,7] In-vivo studies have shown not only greater efficacy of laser-heated probes but

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